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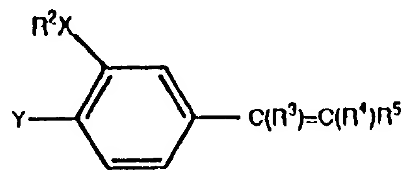
(54) Title: STYRYL DERIVATIVES AND PROCESSES FOR THEIR PREPARATION

(57) Abstract



(I)

Compounds of general formula (I) are described, wherein Y is a halogen atom or a group $-OR^1$, wherein R^1 is an optionally substituted alkyl group; X is -O-, -S- or $-N(R^6)-$, where R^6 is a hydrogen atom or an alkyl group; R^2 is an optionally substituted alkyl, alkenyl, cycloalkyl or cycloalkenyl group; R^3 and R^4, which may be the same or different, is each a group $-(CH_2)_nAr$, where Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms and n is zero or an integer 1, 2 or 3; R^5 is a hydrogen atom or an optionally substituted alkyl group; and the salts, solvates, hydrates and N-oxides thereof. Compounds according to the invention are potent, selective and orally active PDE IV inhibitors and are useful in the prophylaxis and treatment of asthma and other diseases.

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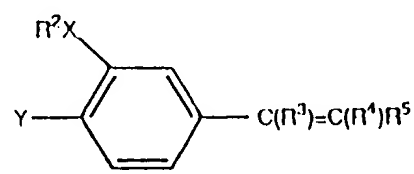
type of PDE isoenzyme in a non-selective manner. Lack of a selective action has been a particular problem given the widespread role of cAMP in vivo and what is needed are potent selective PDE IV inhibitors with an inhibitory action against PDE IV and little or no action against other PDE isoenzymes.

We have now found a novel series of styryl derivatives, members of which compared to known structurally similar compounds are potent inhibitors of PDE IV at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the isolated PDE IV enzyme and also elevate cAMP in isolated leukocytes. Certain compounds prevent inflammation in the lungs induced by carrageenan, platelet-activating factor (PAF), interleukin-5 (IL-5) or antigen challenge. These compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs. Advantageously, compounds according to the invention have good oral activity and at orally effective doses exhibit little or none of the side-effects associated with known PDE IV inhibitors, such as rolipram. The compounds of the invention are therefore of use in medicine, especially in the prophylaxis and treatment of asthma.

Thus according to one aspect of the invention, we provide a compound of formula (1)



(1)

wherein

Y is a halogen atom or a group $-OR^1$, where R^1 is an optionally substituted alkyl group;

X is -0-, -S- or $-N(R^6)-$, where R^6 is a hydrogen atom or an alkyl group.

R^2 is an optionally substituted alkyl, alkenyl, cycloalkyl or cycloalkenyl group;

R^3 and R^4, which may be the same or different, is each a group $-(CH_2)_nAr$, where Ar is a monocyclic or bicylic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms and n is zero or an integer 1, 2 or 3;

R^5 is a hydrogen atom or an optionally substituted alkyl group; and the salts, solvates, hydrates and N-oxides thereof.

The compounds of formula (1) exist as geometrical isomers and the invention extends to all such individual isomers and mixtures thereof. Formula (1) and the formulae hereinafter should be understood to include all individual isomers and mixtures thereof, unless stated otherwise, and even though only one isomer may be depicted.

In the compounds of formula (1), when Y is a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.

When Y in the compounds of formula (1) is a group $-OR^1$, R^1 may be, for example, an optionally substituted straight or branched alkyl group, for example, an optionally substituted C_{1-6}alkyl group, such as a methyl, ethyl, n-propyl, or i-propyl, group. Optional substitutents which may be present on R^1 groups include one or more halogen atoms, e.g. fluorine, or chlorine atoms. Particular substituted alkyl groups include for example $-CH_2F$, $-CH_2Cl$, $-CHF_2$, $-CHCl_2$, $-CF_3$ or $-CCl_3$ groups.

Alkyl groups represented by R^2 or R^5 in the compounds of formula (1) include optionally substituted straight or branched C_{1-6} alkyl groups, e.g. C_{1-3} alkyl groups such as methyl or ethyl groups. Optional substituents on these groups include one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C_{1-6} alkoxy e.g. C_{1-3} alkoxy such as methoxy or ethoxy groups.

Alkenyl groups represented by R^2 in the compounds of formula (1) include optionally substituted straight or branched C_{2-6}alkenyl groups such as ethenyl, propen-1-yl and 2-methylpropen-1-yl. Optional substituents include those described above in relation to the groups R^2 and R^5.

When R^2 in the compounds of formula (1) is an optionally substituted cycloalkyl or cycloalkenyl group it may be for example a C_{3-8}cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C_{3-8} cycloalkenyl group containing for example one or two double bonds such as 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl or 3,5-cyclohexadien-1-yl group, each cycloalkyl or cycloalkenyl group being optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C_{1-6}alkyl e.g. C_{1-3}alkyl such as methyl or ethyl, hydroxyl or C_{1-6}alkoxy e.g. C_{1-3}alkoxy such as methoxy or ethoxy groups.

Alkyl groups represented by R^6 in compounds of formula (1) include straight or branched C_{1-6} alkyl groups, e.g. C_{1-3} alkyl groups such as methyl or ethyl groups.

In the compounds of formula (1) the groups R^3 and/or R^4 may each independently be a group -Ar, -CH_2Ar, -$(CH_2)_2$Ar or -$(CH_2)_3$Ar.

Monocyclic or bicyclic aryl groups represented by the group Ar in compounds of formula (1) include for example C_{6-12} optionally substituted aryl groups, for example optionally substituted phenyl, 1–or 2–naphthyl, indenyl or isoindenyl groups.

When the monocyclic or bicyclic aryl group Ar contains one or more heteroatoms it may be for example a C_{1-9} optionally substituted heteroaryl group containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, Ar heteroaryl groups may be for example monocyclic or bicyclic heteroaryl groups. Monocyclic heteroaryl groups include for example five- or six-membered heteroaryl groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Examples of heteroaryl groups represented by Ar include pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl,

isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl.

The heteroaryl group represented by Ar may be attached to the remainder of the molecule of formula (1) through any ring carbon or heteroatom as appropriate. Thus, for example, when the group Ar is a pyridyl group it may be a 2-pyridyl, 3-pyridyl or 4-pyridyl group. When it is a thienyl group it may be a 2-thienyl or 3-thienyl group, and, similarly, when it is a furyl group it may be a 2-furyl or 3-furyl group.

When in compounds of formula (1) the Ar group is a nitrogen-containing heterocycle it may be possible to form quaternary salts, for example N-alkyl quaternary salts and the invention is to be understood to extend to such salts. Thus for example when the group Ar is a pyridyl group, pyridinium salts may be formed, for example N-alkylpyridinium salts such as N-methylpyridinium.

The aryl or heteroaryl groups represented by Ar in compounds of formula (1) may each optionally be substituted by one, two, three or more substituents [R^7]. The substituent R^7 may be selected from an atom or group R^8 or $-Alk^1(R^8)_m$ wherein R^8 is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-C(O)Alk^1$, $-SO_3H$, $-SO_2Alk^1$, $-SO_2NH_2$, $-SO_2NHAlk^1$, $-SO_2N[Alk^1]_2$, $-CONH_2$, $-CONHAlk^1$, $-CON[Alk^1]_2$, $-NHSO_2H$, $-NHSO_2Alk^1$, $-N[SO_2Alk^1]_2$, $-NHSO_2NH_2$, $-NHSO_2NHAlk^1$, $-NHSO_2N[Alk^1]_2$, $-NHC(O)Alk^1$, or $-NHC(O)OAlk^1$ group; Alk^1 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene chain optionally interrupted by one, two, or three -O-, or -S- atoms or $-S(O)p-$,

[where p is an integer 1 or 2] or $-N(R^6)-$ groups; and m is zero or an integer 1, 2 or 3.

When in the group $-Alk^1(R^8)_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^8 may be present on any suitable carbon atom in $-Alk^1$. Where more than one R^8 substitutent is present these may be the same or different and may be present on the same or different carbon atom in Alk^1. Clearly, when m is zero and no substituent R^8 is present or when Alk^1 forms part of a group such as $-SO_2Alk^1$ the alkylene, alkenylene or alkynylene chain represented by Alk^1 becomes an alkyl, alkenyl or alkynyl group.

When R^8 is a substituted amino group it may be a group $-NH[Alk^1(R^{8a})_m]$ [where Alk^1 and m are as defined above and R^{8a} is as defined above for R^8 but is not a substituted amino, a substituted hydroxyl or a substituted thiol group] or a group $-N[Alk^1(R^{8a})_m]_2$ wherein each $-Alk^1(R^{8a})_m$ group is the same or different.

When R^8 is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^8 is a cycloalkoxy group it may be for example a C_{5-7}cycloalkoxy group such as a cyclopentyloxy or cyclohexyloxy group.

When R^8 is a substituted hydroxyl or substituted thiol group it may be a group $-OAlk^1(R^{8a})_m$ or $-SAlk^1(R^{8a})_m$ respectively, where Alk^1, R^{8a} and m are as just defined.

Esterified carboxyl groups represented by the group R^8 include groups of formula $-CO_2Alk^2$ wherein Alk^2 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl,

1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^2 group include R^7 substituents described above.

When Alk^1 is present in or as a substituent R^7 it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^6)-$ groups.

Particularly useful atoms or groups represented by R^7 include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6} hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C_{1-6}alkylthiol e.g. methylthiol or ethylthiol, C_{1-6}alkoxy, e.g. methoxy or ethoxy, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^2$ [where Alk^2 is as defined above], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. di-methylaminosulphonyl or diethylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino ($-NHSO_2H$), C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylamino-

sulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, C_{1-6}alkanoylamino C_{1-6}alkyl, e.g. acetylaminomethyl or C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.

Where desired, two R^7 substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{2-6}alkylenedioxy group such as ethylenedioxy.

It will be appreciated that where two or more R^7 substituents are present, these need not necessarily be the same atoms and/or groups. The R^7 substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups represented by Ar any substituent may be present at the 2-, 3-, 4-, 5- or 6- positions relative to the ring carbon atom attached to the remainder of the molecule.

In the compounds of formula (1), when an ester group is present, for example a group $-CO_2Alk^2$ this may advantageously be a metabolically labile ester.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as

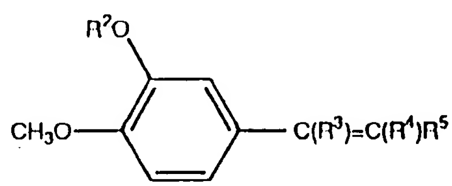
magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In the compounds of formula (1), the group Y is preferably an $-OR^1$ group, especially where R^1 is an optionally substituted ethyl group or, especially, an optionally substituted methyl group. Especially useful substitutents which may be present on R^1 groups include one, two or three fluorine or chlorine atoms.

The group X in compounds of formula (1) is preferably -0-.

A particularly useful group of compounds of formula (1) has the formula (2):



(2)

where R^2 is an optionally substituted cycloalkyl group; R^3, R^4, and R^5 are as defined for formula (1); and the salts, solvates, hydrates and N-oxides thereof.

In the compounds of formulae (1) or (2) R^2 is preferably an optionally substituted methyl or cyclopentyl group. In particular, R^2 is a cyclopentyl group.

In compounds of formulae (1) or (2) the group R^5 is preferably a hydrogen atom.

The group R^3 and R^4 in compounds of formulae (1) or (2) is each preferably a $-CH_2Ar$ group, or, especially an -Ar group.

Particularly useful R^3 or R^4 groups in compounds of formulae (1) or (2) include those R^3 or R^4 groups in which Ar is a monocyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur, or, in particular, nitrogen atoms, and optionally substituted by one, two or more R^7 substituents. In these compounds, when the group represented by Ar is a heteroaryl group it is preferably a nitrogen-containing monocyclic heteroaryl group, especially a six-membered nitrogen-containing heteroaryl group. Thus, in one preferred example, the groups R^4 and R^5 may each be a six-membered nitrogen-containing heteroaryl group. In another preferred example R^4 may be a monocyclic aryl group and R^5 may be a six-membered nitrogen-containing heteroaryl group. In these examples, the six-membered nitrogen-containing heteroaryl group may be an optionally substituted pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group. Particular examples include optionally substituted 2-pyridyl, 3-pyridyl or, especially, 4-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl or 3-pyrazinyl. The monocyclic aryl group may be a phenyl group or a substituted phenyl group.

One particularly useful group of compounds of formulae (1) or (2) is that wherein R^3 and R^4 is each a pyridyl or, especially, a monosubstituted pyridyl, or preferably a disubstituted pyridyl group, or R^3 is a phenyl or substituted phenyl group and R^4 is a pyridyl or, especially a monosubstituted pyridyl, or preferably a disubstituted pyridyl group.

In this particular group of compounds and also in general in compounds of formulae (1) or (2), when R^3 and/or R^4 is a substituted phenyl group it may be for example a mono-, di- or trisubstituted phenyl group in which the substituent is an atom or group R^7 as defined above. When the R^3 and/or R^4 group is a monosubstituted phenyl group the substituent may be in the 2-, or preferably 3-, or especially 4-position relative to the ring carbon atom attached to the remainder of the molecule.

When in compounds of formulae (1) or (2) R^3 and/or R^4 is a substituted pyridyl group it may be for example a mono-or disubstituted pyridyl group,

such as a mono- or disubstituted 2-pyridyl, 3-pyridyl or especially 4-pyridyl group substituted by one or two atoms or groups R^7 as defined above, in particular one or two halogen atoms such as fluorine or chlorine atoms, or methyl, methoxy, hydroxyl or nitro groups. Particularly useful pyridyl groups of these types are 3-monosubstituted-4-pyridyl or 3,5-disubstituted-4-pyridyl, or 2- or 4-monosubstituted-3-pyridyl or 2,4-disubstituted-3-pyridyl groups.

A particularly useful group of compounds according to the invention has the formula (2) wherein R^5 is a hydrogen atom and R^3 and R^4 are as defined for formula (1); and the salts, solvates, hydrates and N-oxides thereof. Compounds of this type in which R^3 is an optionally substituted phenyl, or pyridyl in particular 4-pyridyl, group and R^4 is a pyridyl especially a 4-pyridyl group are particularly preferred.

Particularly useful compounds according to the invention are the (E) and (Z) isomers of

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-furanyl)ethenyl] pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-thienyl)ethenyl] pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]-3-methylimidazole;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] pyridine;

4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl] pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-fluorophenyl-ethenyl] pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-trifluoromethyl-phenyl)ethenyl]pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-methoxyphenyl-ethenyl)]pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-ethenyl]pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-methylphenyl)

ethenyl]pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-methylphenyl)-ethenyl]pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]-3,5-dichloropyridine;
2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] pyridine;
4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl) ethenyl] aniline;
4-[1-(3-Cyclopenxyloxy-4-methoxyphenyl0-2-(4-pyridyl)ethenyl] benzoic acid;
Ethyl N-{4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl) ethenyl]phenyl}carbamate;
N-{4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2(4-pyridyl)ethenyl] phenyl}N'-ethylurea;
N-{4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)]-2-(4-pyridyl)ethenyl} phenylacetamide;
3-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] pyridine;
4-[2-2(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] pyrimidine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-hydroxymethyl-phenyl)ethenyl]pyridine;
4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl] benzamide;
Ethyl-4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-phenyl-ethenyl]benzoate;
N-{4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl] phenyl}methanesulphonamide; or
each (E) or (Z) isomer thereof; and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are selective and potent inhibitors of PDE IV. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of human diseases where an unwanted inflammatory response or muscular spasm (for example bladder or alimentary smooth muscle spasm) is present and where the elevation of cAMP levels may be expected to prevent or alleviate the inflammation and relax muscle.

Particular uses to which the compounds of the invention may be put include the prophylaxis and treatment of asthma, especially inflamed lung associated with asthma, cystic fibrosis, or in the treatment of inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and artherosclerosis.

Compounds of the invention also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

Compounds according to the invention may also elevate cAMP in lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease.

Compounds according to the invention have also been found to reduce gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion.

cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser,

with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

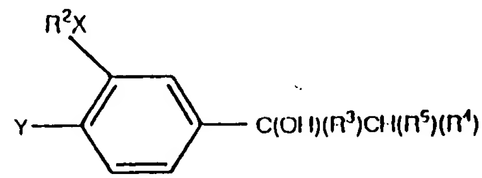
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular inflammatory condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg, e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds according to the invention may be prepared by the following processes. The symbols Y, R^2, R^3, R^4, R^5, and X^1, when used in the formulae below are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio, or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis" John Wiley and Sons, 1981.] It may be that deprotection will form the last step in the synthesis of compounds of formula (1). Thus, in one example, compounds of formula (1) wherein R^3 and/or R^4 contains a carboxylic acid group may be prepared by deprotecting the corresponding compound wherein R^3 and/or R^4 contains a protected carboxyl group, such as an oxazolinyl group, e.g. 4,4-dimethyl-2-oxazolinyl, in the presence of a base, e.g. sodium

hydroxide, in an acid solvent e.g. aqueous hydrochloric acid, at an elevated temperature, e.g. the reflux temperature.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by dehydration of an alcohol of formula (3):



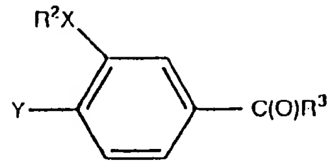
(3)

using an acid or base-catalysed elimination.

Suitable acids include for example phosphoric or sulphonic acids, e.g. 4-toluenesulphonic acid. The reaction may be performed in an inert organic solvent, for example a hydrocarbon such as toluene, at an elevated temperature, for example the reflux temperature. Base catalysed elimination may be performed using for example trifluoroacetic anhydride in the presence of an organic base such as triethylamine at a low temperature e.g. from around 0°C to ambient temperature, in a solvent such as dichloromethane or tetrahydroduran.

In certain instances, the reaction conditions used may also cleave the group R^2 in the starting material of formula (4) to yield a compound of formula (1) where R^2 is a hydrogen atom. Such compounds may be converted to the required compound of formula (3) by a further process according to the invention using a halide R^2Hal (where Hal is a halogen atom such as a bromine or chlorine atom) where necessary in the presence of a base such as caesium or potassium carbonate or an alkoxide such as potassium t-butoxide, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide at ambient temperature or above e.g. around 40°C to 50°C.

Intermediates of formula (3) may be prepared by reaction of a ketone of formula (4):



(4)

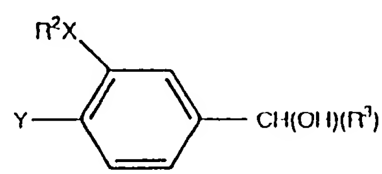
with an organometallic reagent R^4R^5CHZ where Z is a metal atom.

Metal atoms represented by Z include, for example, a lithium atom.

The reaction may be performed in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, at a low temperature, e.g. around -70°C to ambient temperature. This reaction is particularly suitable for the preparation of compounds of formula (1) wherein R^4 is an electron deficient group such as a 2- or 4-pyridyl group.

Reagents R^4R^5CHZ are either known compounds or may be prepared, preferably in situ during the above process, by reaction of a compound $AlkCH_2Z$ [where Alk is an alkyl group such as a n-propyl group] with a compound $R^4R^5CH_2$ where necessary in the presence of a base such as an amine e.g. diisopropylamine using the above-mentioned conditions.

Ketones of formula (4) may be prepared by oxidation of a corresponding alcohol of formula (5):



(5)

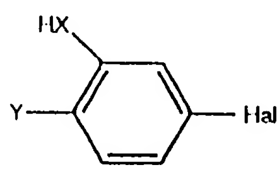
using an oxidising agent such as manganese dioxide in a solvent such as dichloromethane at ambient temperature.

Alternatively, ketones of formula (4) may be prepared by reaction of a halide of formula (6):

using a compound R^2Hal [where Hal is as previously defined] using the reagents and conditions described herein above for the alkylation of intermediates of formula 4.

Intermediates of formula (8) are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

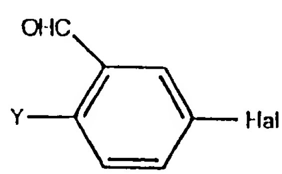
Halides of formula (6) may be prepared by alkylation of a compound of formula (9):



(9)

using the reagents and conditions discussed above in relation to the alkylation of aldehydes of formula (8).

Halides of formula (9) where X is -0- may be prepared by oxidation of an aldehyde of formula (10):

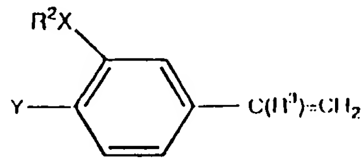


(10)

using an oxidising agent such as 3-chloroperoxybenzoic acid in a halogenated hydrocarbon such as chloroform at a temperature from around 0°C to room temperature.

Aldehydes of formula (8) and halides of formula (10) where X is -S- or -N(R^6)- are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

In yet another aspect of the invention, compounds of formula (1) may be obtained by coupling a compound of formula (11)

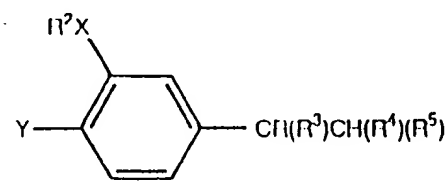


(11)

in a Heck reaction with an organopalladium compound derived from a compound R^4Hal [where Hal is a halogen atom, such as a bromine atom] and a palladium salt, such as palladium acetate, in the presence of a phosphine such as tri-o-tolylphosphine and a base such as triethylamine at an elevated temperature and pressure.

Intermediate alkenes of formula (11) may be obtained by reaction of a corresponding ketone of formula (4) (described herein above) using a Wittig reaction employing a phosphonium salt such as methyltriphenylphosphonium bromide in the presence of a base such as n-butyllithium and in inert solvent such as tetrhydrofuran at, for example, 0°C to ambient temperature.

In a further process according to the invention a compound of formula (1) may be prepared by dehydrogenation of a compound of formula (12):

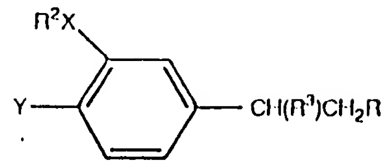


(12)

where R is a hydrogen atom, using a dehydrogenating reagent.

Suitable dehydrogenating reagents include for example quinones such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, in a solvent, e.g. dioxane, at an elevated temperature, e.g. the reflux temperature.

Compounds of formula (12) may be prepared by cyclisation of a compound of formula (13)



(13)

where R is a carboxylic acid [$-CO_2H$] group or a reactive derivative thereof; or a nitrile [-CN] or an imine salt with a bifunctional reagent $W^1R^{4a}W^2$ and, where necessary, a compound $R^{4b}W^3$ [where W^1, W^2 and W^3, which may be the same or different, is each a reactive functional group or a protected derivative thereof; and R^{4a} and R^{4b} are components of the heteroaryl group R^4 such that when added together with W^1, W^2 and W^3 to the group R in compounds of formula (15) the resulting group $-RW^1R^{4a}W^2$ or $-RW^1R^{4a}W^2R^{4b}W^3$ constitutes the heteroaryl group R^4].

Reactive derivatives of carboxylic acids for use in this reaction include acid halides, (e.g. acid chlorides), amides, including thioamides, or esters, including thioesters. Imine salts include for example salts of formula [e.g.-$C(OAlk)=NH_2^+A^-$, where Alk is a C_{1-4}alkyl group and A^- is a counterion e.g. a chloride ion].

In this general reaction the reactive functional groups represented by W^1, W^2 or W^3 may be any suitable carbon, nitrogen, sulphur or oxygen nucleophiles. Particular examples include simple nucleophiles such as carbanions [e.g. generated by the coupling of an alkyl group with an organometallic compound], amino, thiol and hydroxyl groups.

In general, the cyclisation reaction will initially be performed in a solvent, for example an inert solvent such as a halocarbon, e.g. dichloromethane, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a hydrocarbon, e.g. an aromatic hydrocarbon such as toluene, from a low temperature, e.g. around -70°C, to around the reflux temperature, where necessary in the presence of a base or a thiation reagent, e.g. Lawesson's reagent,

followed if necessary by heating, to an elevated temperature, e.g. the reflux temperature.

Thus, in one particular example, compounds of formula (12) wherein R^4 is a benzothiazolyl, benzoxazolyl or benzimidazolyl group may be prepared by reaction of a compound of formula (13) where R is an acid halide, e.g. acid chloride, with a reagent $W^1R^{4a}W^2$ which is 2-aminothiophenol, 2-hydroxyphenol, or 1,2-diaminobenzene respectively in the presence of a base e.g. an organic amine such as pyridine, in a solvent e.g. a halocarbon such as dichloromethane, from around -70°C to the reflux temperature..

In another example of the general cyclisation process, a compound of formula (13) where R is an acid halide as described above may be reacted with a compound $W^1R^{4a}W^2$ which is a monoalkylmalonate, e.g. ethyl hydrogen malonate, followed by reaction with a compound $R^{4b}W^3$ which is hydrazine to give a compound of formula (1) wherein R^4 is a 5-hydroxypyrazolyl group.

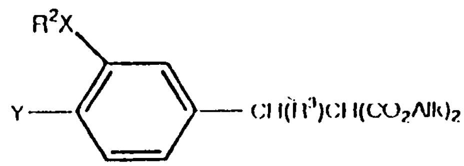
In another variation of the cyclisation process, the halide of formula (13) may be reacted with a compound $W^1R^{4a}W^2$ which is $BrMg(CH_2)_3[-O(CH_2)_2O-]$ followed by reaction in an acid solution with a compound $R^{4b}W^3$ which is methylamine to yield a compound of formula (1) wherein R^4 is a N-methyl pyrrole group.

In a further example of the cyclisation process, the halide of formula (13) may be reacted with a compound $W^1R^{4a}W^2$ which is $H_2NNHCSNH_2$ in an aromatic hydrocarbon such as toluene, at an elevated temperature, e.g. around 150°C, followed by treatment with a base, e.g. an inorganic base such as sodium bicarbonate to give a compound of formula (12) wherein R^4 is a 1,2,4-triazolyl-5-thiolate group.

Intermediate compounds of formula (13) are particularly useful and form a further aspect of the invention. Active derivatives of the acids of formula (13) and other compounds of formula (13) where R is a nitrile or an imine salt may be prepared from the corresponding acids [where R is $-CO_2H$]

using conventional procedures for converting carboxylic acids to such compounds, for example as described in the Examples hereinafter.

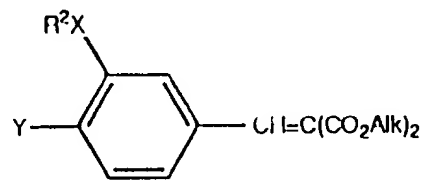
Acids of formula (13) [where R is $-CO_2H$] may be prepared by hydrolysing a diester of formula (14)



(14)

where Alk is a C_{1-4}alkyl group, e.g. an ethyl group, with a base, e.g. sodium hydroxide, in a solvent, e.g. dioxane, at an elevated temperature, e.g. the reflux temperature, followed by acidification at an elevated temperature.

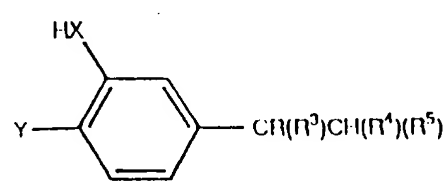
Diesters of formula (14) may be prepared by reacting a diester of formula (15)



(15)

with an organometallic reagent, such as a Grignard reagent using the conditions described above for the preparation of alcohols of formula (3) (where R is a hydroxy group).

In another process according to the invention, a compound of formula (12) may be prepared by alkylation of a compound of formula (16):



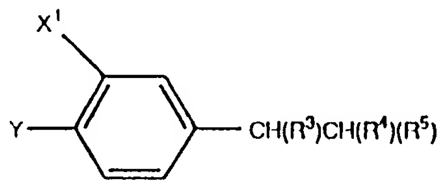
(16)

using a reagent R^2L, where L is a leaving group.

Leaving groups represented by L include halogen atoms such as iodine or chlorine or bromine atoms or sulphonyloxy groups such as arylsulphonyloxy groups, e.g. p-toluenesulphonyloxy.

The alkylation reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium-t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at ambient temperature or above e.g. around 40°C to 50°C.

Intermediates of formula (16) may be obtained from the corresponding protected compound of formula (17):



(17)

wherein X^1 is a protected hydroxy, thio or amino group using conventional procedures [see Green, T. W. *ibid*]. Thus, for example, where X is a t-butyldimethylsilyloxy group, the required hydroxyl group may be obtained by treatment of the protected intermediate with tetrabutylammonium fluoride. The protected intermediate of formula (16) may be prepared in an analogous manner to the compounds of formula (1) using the reactions described herein and appropriately protected intermediates.

Compounds of formula (15) may be prepared by condensing an aldehyde of formula (7) with a malonate, e.g. diethylmalonate, if necessary in the presence of catalysts, e.g. piperidine and acetic acid, in an inert solvent, e.g. toluene, at elevated temperature, e.g. the reflux temperature.

Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1). Thus, for example, a group represented by R^3 or R^4 in compounds of formula (1) may be substituted in the aryl or

heteroaryl portions by any of the groups R^7 by an appropriate substitution reaction using the corresponding unsubstituted compound of formula (1) and a R^7 containing nucleophile or electrophile.

In another example of an interconversion process a compound of formula (1) wherein the aryl or heteroaryl group in R^3 or R^4 contains a $-CH_2NH_2$ substituent may be prepared by reduction of a corresponding compound wherein R^5 contains a nitrile group, using for example a complex metal hydride such as lithium aluminium hydride in a solvent such as an ether e.g. diethylether.

In a further example, a compound of formula (1) wherein the aryl or heteroaryl group in R^3 and/or R^4 contains an alkanoylamino or alkanoylaminoalkyl substituent may be prepared by acylation of a corresponding compound wherein R^3 and/or R^4 contains a $-NH_2$ or alkylamino group by reaction with an acyl halide in the presence of a base, such as a tertiary amine e.g. triethylamine in a solvent such as dichloromethane.

In yet another example of an interconversion process, compounds of formula (1) wherein R^3 and/or R^4 is substituted by an ester [CO_2Alk^2], e.g. an ethanoate, may be prepared by esterification of a corresponding compound wherein R^3 and/or R^4 contains a carboxylic acid, using an acid halide, such as an acid chloride, e.g. acetyl chloride, in an alcohol, such as ethanol, at an elevated temperature, such as the reflux temperature.

Compounds of formula (1) wherein R^3 and/or R^4 is substituted by a carboxylic acid may be prepared from the corresponding compound wherein R^3 and/or R^4 contains a formyl group, by oxidation with an oxidising agent, e.g. potassium permanganate, in a solvent, such as an alcohol, e.g. tert-butanol, at ambient temperature.

In a further interconversion reaction, compounds of formula (1) wherein R^3 and/or R^4 is substituted by an aminoalkyl group, such as dimethylaminomethyl, may be prepared by reductive amination of a corresponding compound wherein R^3 and/or R^4 contains a formyl group, using an amine,

(3-cyclopentyloxy-4-methoxyphenyl)-1-phenylmethanol (13.4g) as a white solid. m.p. 82.5-83°C; δ_H ($CDCl_3$) 1.5-2.0 (8H, br, m, ($C\underline{H}_2)_4$), 2.30 (1H, br, s, O$\underline{H}$), 3.77 (3H, s, O$\underline{Me}$), 4.68 (1H, br, m, OC$\underline{H}$CH$_2$), 5.77 (1H, s, C$\underline{H}$OH), 6.75-6.85 (3H, m, Ar$\underline{H}$ ortho to OMe + 2xAr$\underline{H}$ meta to OMe), and 7.15-7.4 (5H, m, C_6H_5); m/z 298 (M^+ 20%), 230 (50), 151 (30), 125 (100), 124 (33), 105 (38), and 92 (22).

The alcohol (prepared above) (13.4g, 44.8mmol) was dissolved in CH_2Cl_2 (150ml) and treated with MnO_2 (22g). The reaction mixture was vigorously stirred at RT for 18h then treated with a further portion of MnO_2 (20g). More MnO_2 (20g) was added after 10h and the mixture stirred for 18h then filtered through Celite® and concentrated *in vacuo*. The residue was recrystallised from EtOH to afford the title compound (11.27g; two crops) as a white crystalline solid m.p. 59-75°C; δ_H ($CDCl_3$) 1.5-2.1 (8H, br, m, ($C\underline{H}_2)_4$), 3.88 (3H, s, OMe), 4.80 (1H, br m, OC$\underline{H}$CH$_2$), 6.83 (1H, d, *J* 8.5 Hz, Ar$\underline{H}$ ortho to OMe), and 7.25-7.8 (7H, m, 2xAr$\underline{H}$ meta to OMe + $C_6\underline{H}_5$); m/z 296 (M^+ 11%), 229 (17), 228 (95), 152 (12), 151 (100), 105 (30), 77 (21), and 41 (10).

The following intermediate was prepared in a manner similar to Intermediate 2a.

b) **(3-Cyclopentyloxy-4-methoxyphenyl)(2-methoxyphenyl)ketone**

From Intermediate 4 (1.35g, 5.0mmol) and 2-methoxybenzaldehyde (0.68g, 5.0mmol). Chromatography (SiO_2; EtOAc/hexane, 1:1) afforded the title compound (1.43g) as a white solid (Found: C, 73.53, H, 6.86. $C_{20}H_{22}O_4$ requires C, 73.60; H, 6.79%); m/z (EI) 326 (M^+, 28%), 258 (65), 241 (82), 151 (67), 138 (32), 135 (100), and 121 (45).

INTERMEDIATE 3

5-Bromo-2-methoxyphenol

A solution of 5-bromo-2-methoxybenzaldehyde (100g, 0.46mol) in $CHCl_3$ (250ml) was cooled with an ice bath and 3-chloroperoxybenzoic acid (50-60% purity) (146g, 0.51mol) in $CHCl_3$ (1000ml) added. The reaction mixture was allowed to warm slowly to room temperature and stirred for 72h. The white solid was filtered off and the filtrate concentrated *in vacuo*. The residue was dissolved in Et_2O (200ml) and washed with 1M sodium

sulphite solution (2x200ml) then $NaHCO_3$ [half saturated] (3x200ml). The ether layer was washed with 10% aqueous NaOH (3x100ml) and the combined basic extract was acidified with concentrated hydrochloric acid and extracted with Et_2O (3x100ml). The combined organic extract was dried ($MgSO_4$) and florisil (10g) filtered and the solvent removed under reduced pressure to give the title compound (90g) as a pale brown solid.

INTERMEDIATE 4

4-Bromo-2-cyclopentyloxyanisole

Intermediate 3 (90g)was dissolved in DMF (300ml), and treated with Cs_2CO_3 (158g, 490mmol), and cyclopentyl bromide (73g, 52.5ml, 490mmol). After stirring overnight, further Cs_2CO_3 (35g, 107mmol) and cyclopentylbromide (12ml, 16.7g, 112mmol) were added and stirring continued for 2h. Further portions of cyclopentylbromide (10ml) and Cs_2CO_3 were then added (14g). After stirring for 1h, the DMF was evaporated *in vacuo* and the residue diluted with water (200 ml) and extracted with Et_2O (3x100ml). The combined organic extract was washed with NaOH solution (5%, 2x100ml), water (100ml), then dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give a red oil which was distilled (140°C, 0.3mbar) to afford the title compound (101g) as a colourless oil (Found: C, 53.11; H, 5.53. $C_{12}H_{15}BrO_2$ requires C, 53.15; H, 5.58%).

INTERMEDIATE 5

(3-Cyclopentyloxy-4-methoxyphenyl)(4-pyridyl)ketone

n-BuLi (1.45M in hexanes; 19.6ml, 28.4mmol) was added dropwise at -70°C to a solution of Intermediate 4(7.0g, 25.8mmol) in THF (50ml). After stirring for 0.25h, a solution of 4-cyanopyridine (3.08g, 29.7mmol) in THF (15ml) was added and maintained at -70°C for 0.75h. The reaction mixture was then allowed to warm to -10°C and quenched with aqueous HCl (10%; 60ml). The mixture was stirred for 0.5h, basified with aqueous NaOH (10%, 70ml), and extracted with Et_2O (3x70ml). The extract was washed with brine (100ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; EtOAc/hexane, 4:1) to afford the title compound (6.34g) as a white powder. δ_H ($CDCl_3$) 1.5-1.9 (8H, br m, $(CH_2)_4$), 3.90 (3H, s, OMe), 4.82 (1H, br m, $OCHCH_2$), 6.84 (1H, d, *J* 8.4 Hz, ArH *ortho* to OMe) 7.29 (1H, dd, *J* 8.4, 2.0 Hz, ArH *para*

to cyclopentyloxy), 7.4-7.55 (3H, m, Ar<u>H</u> *ortho* to cyclopentyloxy + pyridine $\underline{H}_3$, $\underline{H}_5$), and 8.73 (2H, dd, *J* 4.4 Hz, 1.5 Hz, pyridine $\underline{H}_2$, $\underline{H}_6$).

INTERMEDIATE 6

(E) and (Z) Isomers of 4-[1-(3-Hydroxy-4-methoxyphenyl)-2-(4-pyridyl) ethenyl]pyridine

Intermediate 8 (0.72g, 1.85mmol) in toluene (120ml) containing 4-toluenesulphonic acid (0.88g, 4.6mmol) was heated to reflux in a Dean-Stark apparatus for 18h. The cooled reaction mixture was treated with aqueous NaOH (10%) then taken to pH 7 with concentrated hydrochloric acid. The mixture was extracted with CH_2Cl_2 (3x40ml), the extract washed with saturated $NaHCO_3$ (100ml), and Na_2CO_3 (10%;2x60ml), then dried ($MgSO_4$), and concentrated *in vacuo* to afford the title compound (0.4g) as a yellow foam; δ_H ($CDCl_3$) (major isomer) 3.88 (3H, s, O<u>Me</u>), 6.6-6.9 (6H, m, Ar<u>H</u> *ortho* to OMe + 2xAr<u>H</u> *meta* to OMe + C=C<u>H</u> + pyridine $\underline{H}_3$, $\underline{H}_5$), 7.08 (2H, dd, *J* 4.6, 1.6 Hz, pyridine $\underline{H}_3$, $\underline{H}_5$), 8.30 (2H, dd, *J* 4.5, 1.6 Hz, pyridine $\underline{H}_2$, $\underline{H}_6$), and 8.51 (2H, dd, *J* 4.4, 1.6 Hz, pyridine $\underline{H}_2$, $\underline{H}_6$), [the minor isomer displays a signal at δ 3.90 (3H, s, O<u>Me</u>)].

INTERMEDIATE 7

a) **(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-2-phenylethyl] pyridine**

n-BuLi (1.4*M* in hexanes; 2.7ml, 3.7mmol) was added dropwise at -70°C to a solution of 4-methylpyridine (0.35g, 3.72mmol) in THF (20ml). After 0.5h, a solution of Intermediate 2 (1.00g, 3.38mmol) in THF (4ml) was added over 5 min at -70°C, the mixture stirred for 1h at this temperature then allowed to warm to RT over 2h. The reaction mixture was partitioned between Et_2O (50ml) and water (50ml) and the organic layer was separated. The aqueous layer was further extracted with Et_2O (2x40ml) and the combined organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; EtOAc-hexane) to afford, first, Intermediate 2 (300mg) then the title compound (738mg) as a white solid. m.p. 148-149°C (toluene-hexane) (Found : C, 77.32; H, 7.04; N, 3.50. $C_{25}H_{27}O_3$ requires C, 77.09; H, 6.99; N, 3.60%); δ_H ($CDCl_3$) 1.4-1.9 (8H, br, m, $(C\underline{H}_2)_4$), 2.3 (1H, v.br.s, O<u>H</u> exchanges with D_2O), 3.51 (2H, s, $C\underline{H}_2$ pyridine), 3.78 (3H, s, O<u>Me</u>), 4.60 (1H, br, m,

OC<u>H</u>CH$_2$), 6.65-6.9 (5H, m) and 7.15-7.4 (5H, m) (Ar<u>H</u> ortho to OMe + 2xAr<u>H</u> meta to OMe + C_6H_5+ pyridine H_3, H_5), and 8.22 (2H, dm, J 4.5Hz, pyridine H_2, H_6); m/z 389 (M$^+$ 3%), 298 (15), 297 (69), 229 (27), 228 (37), 151 (43), 105 (100), 93 (52), 77 (24), and 41 (14).

The following compounds were prepared in a manner similar to Intermediate 7a.

b) **(±)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-2-phenylethyl] pyrazine**

From 2-methylpyrazine (1.0ml, 110mmol) and Intermediate 2 (3.24g, 11.0mmol). Trituration with Et_2O gave the title compound (0.885g) as a white solid. δ_H ($CDCl_3$) 1.45-1.9 (8H, br, m, $(CH_2)_4$), 3.73 (2H, s, CH_2 pyrazine), 3.80 (3H, s, OMe), 4.68 (1H, br, m, OCH), 6.22 (1H, br s, OH), 6.73 (1H, d, J 8.4 Hz, ArH ortho to OMe), 6.89 (1H, dd, J 8.4, 2.0Hz, ArH para to cyclopentyloxy), 7.0 (1H, d, J 2.0Hz, ArH ortho to cyclopentyloxy, 7.1-7.5 (5H, m, C_6H_5), and 8.37 (3H, s, pyrazine H_3, H_5 H_6).

c) **(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-phenylethyl]-3,5-dichloropyridine**

From Intermediate 11 (2.0g, 12.3mmol) and Intermediate 2 (3.65g, 12.3mmol). Purification by column chromatography (SiO_2;0-2% MeOH/ CH_2Cl_2) afforded the title compound (1.74g) as a white solid. m.p. 129-130°C. δ_H ($CDCl_3$) 1.5-1.9 (8H, br, m, $(CH_2)_4$), 2.65 (1H, br s, OH), 3.85 (3H, s, OMe), 3.92 (1H, d, J 14Hz, CH_AH_B pyridine), 3.98 (1H, d, J 14 Hz, CH_AH_B pyridine), 4.57 (1H, br, m, OCH), 6.7-6.9 (3H, m, ArH ortho + 2x ArH meta to OMe), 7.2-7.4 (5H, m, C_6H_5), and 8.36 (2H, s, pyridine H_2, H_6).

d) **4-[2-(4-Bromophenyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyridine**

From 4-picoline (2.0ml, 1.90g, 20.4mmol) and Intermediate 26 (7.30g, 19.5mmol). Purification by column chromatography (SiO_2; gradient elution 50-75%, EtOAc/hexane) gave the title compound (7.77g) as a pale yellow foamy solid. Found: C, 63.82; H, 5.58; N, 2.96. $C_{25}H_{26}BrNO_3$ requires C, 64.11; H, 5.60; N, 2.99%. δ_H ($CDCl_3$) 1.5-1.9 (8H, br, m, $(CH_2)_4$), 2.7

(1H, br s, O<u>H</u>), 3.46 (1H, d, <u>J</u> 13.1Hz, C<u>H</u>$_A$H$_B$ pyridine), 3.54 (1H, d, <u>J</u> 13.1 Hz, CH$_A$<u>H</u>$_B$ pyridine), 3.82 (3H, s, O<u>Me</u>), 4.64 (1H, br m, OC<u>H</u>), 6.75-6.9 (5H, m, C_6H_3 + pyridine <u>H</u>$_3$, <u>H</u>$_5$), 7.21 (2H, <u>ca.</u> d, <u>J</u> 8.7Hz, Ar<u>H</u> of C_6H_4), and 8.29 (2H, <u>ca</u>. d, <u>J</u> 6.0Hz, pyridine <u>H</u>$_2$, <u>H</u>$_6$); $\nu_{max.}$ ($CDCl_3$) 3604, 1605, 1513, and 1256 cm^{-1}; <u>m/z</u> (ESI) 470 (<u>M</u>$^+$ +2, 20%), 468 (<u>M</u>$^+$, 18), 377 (52), 375 (55), 95 (13), and 91 (100).

e) **<u>(±)-4-{2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-[4-(4,4-dimethyl-2-oxazolinyl)phenyl]-2-hydroxyethyl}pyridine</u>**

From 4-methylpyridine (1.45g, 1.52ml, 15.6mmol) and Intermediate 14 (5.82g, 14.9mmol). Trituration with Et_2O gave the <u>title compound</u> (6.61g) as an off-white solid. δ_H ($CDCl_3$) 1.37 (6H, s, C<u>Me</u>), 1.55-1.8 (8H, m, (C<u>H</u>$_2$)$_4$), 2.7 (1H, v. br s, O<u>H</u>), 3.56 (2H, br s, C<u>H</u>$_2$ pyridine), 3.82 (3H, s, O<u>Me</u>), 4.10 (2H, s, oxazoline C<u>H</u>$_2$), 4.63 (1H, m, OC<u>H</u>), 6.75-6.9 (5H, m, Ar<u>H</u>), 7.37 (2H, d, <u>J</u> 8.6Hz, pyridine <u>H</u>$_3$, <u>H</u>$_5$), 7.85 (2H, d, <u>J</u> 7.3Hz, Ar<u>H</u> <u>ortho</u> to oxazoline) and 8.29 (2H, br s, pyridine <u>H</u>$_2$, <u>H</u>$_6$); $\nu_{max.}$ ($CDCl_3$) 3603, 1649, 1512, and 1257 cm^{-1}; <u>m/z</u> (ESI) 487 (<u>M</u>$^+$ +1, 100%), and 394 (61).

f) **<u>4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-2-(2-thienyl)ethyl]pyridine</u>**

From 4-picoline (0.94g, 10.1mmol) in THF (80ml) and Intermediate 18 (3.06g, 10.1mmol) in THF (20ml). Chromatography (SiO_2; Et_2O to EtOAc/hexane, 4:1) afforded the <u>title compound</u> (3.32g) as a white foam m.p. 57-67°C (Found C, 69.82; H, 6.42; N, 3.41. $C_{23}H_{25}NO_3S$ requires C, 69.85; H, 6.37; N, 3.54%); δ_H ($CDCl_3$) 1.5-2.0 (8H, m, (C<u>H</u>$_2$)$_4$), 3.0 (1H, br s, O<u>H</u>), 3.50 (1H, d, <u>J</u> 13.2Hz pyridine C<u>H</u>$_A$H$_B$), 3.58 (1H, d, <u>J</u> 13.2Hz, pyridine CH$_A$<u>H</u>$_B$), 3.83 (3H, s, O<u>Me</u>), 4.64 (1H, m, OC<u>H</u>),6.75-6.8 (1H, m, Ar<u>H</u> of C_6H_3), 6.85-7.05 (6H, m, 2xAr<u>H</u> of C_6H_3 + pyridine <u>H</u>$_3$, <u>H</u>$_5$ + thiophene <u>H</u>$_3$, <u>H</u>$_4$), 7.25 (1H, dd, <u>J</u> 4.7, 1.7Hz, thiophene <u>H</u>$_5$), and 8.29 (2H, <u>ca</u> d, <u>J</u> 6.0Hz, pyridine <u>H</u>$_2$, <u>H</u>$_6$); <u>m/z</u> (ESI) 418 (<u>M</u>$^+$ + Na, 10%), 396 ((<u>M</u>$^+$ + 1, 100), 303 (35), 95 (12), and 94 (72).

The alcohol was then dehydrated using the procedure described in Example 7.

INTERMEDIATE 8

(±)-4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-1-hydroxy-2-(4-pyridyl) ethyl]pyridine

n-BuLi (1.45M in hexanes; 5.1ml, 7.41mmol) was added dropwise at -70°C to a solution of 4-methylpyridine (0.69g, 7.41mmol) in THF (20ml). After 0.5h a solution of Intermediate 5 (2.0g, 6.73mmol) in THF (10ml) was added dropwise over 5 min. The reaction mixture was stirred for 0.5h at -70°C then at RT for 0.5h. Water (50ml) was added and the mixture extracted with EtOAc (3x60ml). The extract was washed with brine (80ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; EtOAc to EtOAc/CH_3OH, 9:1) to afford the title compound (2.33g) as a white amorphous solid m.p. 99-103°C; δ_H ($CDCl_3$) 1.5-2.0 (9H, br, m, $(CH_2)_4$ + OH), 3.49 (2H, d, J 2.3 Hz, CH_2 COH), 4.65 (1H, br m, $OCHCH_2$), 6.7-6.9 (5H, m, ArH ortho to OMe+ 2xArH meta to OMe + pyridine H_3, H_5), 7.20 (2H, dd, J 4.6, 1.6 Hz, pyridine H_3, H_5), 8.22 (2H, dd, J 4.6, 1.6 Hz, pyridine H_2, H_6), and 8.40 (2H, dd, J 4.6, 1.6 Hz, pyridine H_2, H_6); m/z 390 (M^+ 3%), 298 (21), 297 (14), 230 (21), 229 (91), 151 (100), 106 (22), 93 (27), 78 (12), and 41 (23).

INTERMEDIATE 9

1-(3-Cyclopentyloxy-4-methoxyphenyl)-1-phenylethene

To a cold suspension (0°C) of methyl triphenylphosphonium bromide (53.6g; 0.15mol) in THF (500ml) under a nitrogen atmosphere was added n-BuLi (1.6M in hexanes; 94ml, 0.15mol) dropwise and the reaction mixture stirred at 0°C for 1h. A solution of Intermediate 2 (29.6g, 0.1mol) in THF (100ml) was added dropwise and the stirred reaction mixture allowed to warm to RT over 3h. The mixture was poured into 10% NH_4Cl solution (600ml) and extracted with CH_2Cl_2 (2x500ml). The combined organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual slurry was triturated with hot hexane (500ml), the precipitated phosphine oxide filtered off and the filtrate evaporated *in vacuo* to yield the title compound (28.85g) as a yellow oil. δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.85 (3H, s, OMe), 4.71 (1H, br m, OCH), 5.38 (2H, dd, J 10.5, 1.3Hz, $C{=}CH_2$), 6.75-6.9 (3H, m, C_6H_3), and 7.3-7.5 (5H, m, C_6H_5).

INTERMEDIATE 10

a) **(±)-3-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-2-phenylethyl]-2-methoxypyrazine**

n-BuLi (1.6M in hexanes; 6ml, 12mmol) was added dropwise at 4°C to a solution of N, N-diisopropylamine (1.85ml, 13mmol) in THF (40ml). After 0.5h, 2-methoxy-3-methylpyrazine (1.28ml, 11mmol) was added dropwise at -70°C and the mixture stirred for 2h at this temperature. A solution of Intermediate 2 (3.26g, 11mmol) in THF (20ml) was added over 10 min at -70°C and the mixture stirred for a further 1h and then allowed to warm to RT. The reaction mixture was partitioned between CH_2Cl_2 (75ml) and saturated $NaHCO_3$ (100ml). The organic layer was separated, combined with further CH_2Cl_2 extracts (2x75ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; CH_2Cl_2) to afford the title compound (2.94g) as a white foam. δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.63 (1H, d, J 14 Hz, CHH pyrazine), 3.77 (1H, d, J 14Hz, CHH pyrazine), 3.79 (3H, s, OMe ortho to cyclopentyloxy), 3.97 (3H, s, pyrazine OMe), 4.67 (1H, br m, OCH), 6.72 (1H, dd, J 8.4Hz, ArH ortho to OMe), 6.77 (1H, s, OH), 6.91 (1H, dd, J 8.4Hz, 2.0Hz, ArH para to cyclopentyloxy), 7.00 (1H, d, J 2.0Hz, ArH ortho to cyclopentyloxy), 7.1-7.5 (5H, m, C_6H_5), and 7.85-7.95 (2H, m, pyrazine H_5, H_6).

b) **(±)-2-[-2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-2-phenylethyl]-4-methylpyridine**

From 2,4-dimethylpyridine (1.7ml, 14.5mmol) and Intermediate 2 (4.30g, 14.5mmol). Purification by chromatography (SiO_2; CH_2Cl_2) afforded the title compound (1.23g) as a colourless oil (Found: C, 77.07; H, 7.10; N, 3.25. $C_{26}H_{29}NO_3$ requires C, 77.39; H, 7.24; N, 3.47%); δ_H ($CDCl_3$) 1.4-1.9 (8H, br m, $(CH_2)_4$), 2.25 (3H, s, pyridine Me), 3.60 (2H, s, CH_2 pyridine), 3.77 (3H, s, OMe), 4.68 (1H, br m, OCH), 6.72 (1H, d; J 8.5Hz, ArH ortho to OMe), 6.8-6.95 (3H, m, ArH para to cyclopentyloxy + pyridine H_3, H_5), 7.02 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy), 7.1-7.3 (3H, m, meta and para ArH of C_6H_5), 7.46 (2H, ca d, J 8.5Hz, ortho ArH of C_6H_5), and 8.23 (1H, ca d, J 6 Hz, pyridine H_6); m/z (ESI) 404 (M^++1, 72%), 387 (13), and 386 (100).

c) **(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-2-phenylethyl]pyrimidine**

From 4-methylpyrimidine (1.0ml) and Intermediate 2 (3.98g). Purification by chromatography (SiO_2;CH_2Cl_2) afforded the title compound (2.56g) as a white solid; δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.66 (2H, s, CH_2 pyrimidine), 3.77 (3H, s, OMe), 4.65 (1H, br m, OCH), 6.58 (1H, s, OH), 6.72 (1H, d, *J* 8.4Hz, ArH *ortho* to OMe), 6.85 (1H, dd, *J* 8.4, 2.2Hz, ArH *para* to cyclopentyloxy), 6.98 (1H, d, *J* 2.2Hz, ArH *ortho* to cyclopentyloxy), 7.07 (1H, d, *J* 5.2Hz, pyrimidine H_5), 7.15-7.45 (5H, m, C_6H_5), 8.53 (1H, d, *J* 5.2Hz, pyrimidine H_6), and 8.99 (1H, s, pyrimidine H_2).

d) **(±)-3-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-2-phenylethyl]pyridazine**

From 3-methylpyridazine (1.0ml) and Intermediate 2 (3.98g). Purification by chromatography (SiO_2; EtOH-CH_2Cl_2) afforded the title compound (4.02g) as an off-white solid.

INTERMEDIATE 11

3,5-Dichloro-4-methylpyridine

3,5-Dichloropyridine (2.04g, 13.5mmol) in THF (5ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (1.9ml, 13.5mmol) and *n*-BuLi (1.6*M*; 8.4ml, 13.5mmol)] in THF (25ml) at -70°C. After stirring at this temperature for 5 min, iodomethane (0.85ml, 13.5 mmol) was added and the reaction mixture stirred for a further 1.5h at -70°C. Saturated $NaHCO_3$ (20ml) and CH_2Cl_2 (20ml) were added, the organic phase separated, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; Et_2O/hexane, 1:3) to afford the title compound (1.16g) as a pale yellow solid. δ_H ($CDCl_3$) 2.46 (3H, s, Me), and 8.36 (2H, s, pyridine H_2, H_6).

INTERMEDIATE 12

(4-Bromophenyl)(3-cyclopentyloxy-4-methoxyphenyl)ketone

A solution of Intermediate 4 (8.00g, 29.5mmol) in THF (50ml) at -70°C was treated with *n*-BuLi (19.4ml, 31.0mmol, 1.6*M* solution in hexanes). The slightly yellow solution was stirred at -70°C for 0.5h then a solution of 4-bromobenzaldehyde (5.46g, 29.5mmol) in THF (50ml) was added *via* cannula. The reaction was allowed to warm to RT over 2h then quenched with water (25ml) and extracted with Et_2O (2x50ml). The extract was dried

d, J 6.2Hz, pyridine H_3, H_5), 7.23, 7.38 (2H, d, J 8.2Hz, ArH), 7.9-8.0 (2H, m, ArH) and 8.3-8.45 (2H, m, pyridine H_2, H_6); ν_{max} ($CDCl_3$)1735, 1646, 1597 and 1318 cm^{-1}; m/z (ESI) 469 (M^+,100%).

INTERMEDIATE 16

(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-furyl)-2-hydroxyethyl]pyridine

n-Butyllithium (1.6M solution in hexane; 16.9ml, 27mmol) was added to a stirred solution of furan (1.84g, 1.96ml, 27mmol) in THF (25ml) at -70°C. After 1h at -70°C, a solution of Intermediate 1 (4.0g, 18mmol) in THF (10ml) was added over 10 min. The reaction mixture was stirred at -70°C for 0.75h, warmed to RT over 0.75h, then quenched with water (100ml) and extracted with Et_2O (3x60ml). The extract was washed with brine (100ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residual orange-yellow oil was subjected to chromatography (SiO_2; CH_2Cl_2/hexane, 3:1, then Et_2O/hexane, 1:1) to give (3-cyclopentyloxy-4-methoxyphenyl)(2-furyl)methanol (3.2g, 61%) as a colourless unstable oil; $\nu_{max.}$ (neat) 3500cm^{-1}.

The alcohol (3.2g) was stirred with manganese (IV) oxide (10g) in CH_2Cl_2 (100ml) at RT for 3h. The mixture was filtered through Celite® and the filtrate concentrated *in vacuo*. The residual dark oil was subjected to chromatography (SiO_2) to give (3-cyclopentyloxy-4-methoxyphenyl)-(2-furyl)ketone (1.9g); ν_{max} (neat) 1620cm^{-1}

n-Butyllithium (1.6M solution in hexanes; 4.2ml, 6.64mmol) was added to a solution of a 4-methylpyridine (0.62g, 0.65ml, 6.64mmol) in THF (25ml) at -70°C. After 0.5h, a solution of the crude ketone (1.9g, ca. 6.6mmol) in THF (5ml) was added, stirred for 1h at -70°C, then at RT for 0.25h. The reaction mixture was quenched with water (50ml) and extracted with EtOAc (3x50ml). The extract was dried ($MgSO_4$), concentrated *in vacuo*, and the residual red oil subjected to chromatography (SiO_2; EtOAc/hexane, 3:2) to afford the title compound (1.23g, 49%) as a pale yellow oil; δ_H ($CDCl_3$) 1.5-1.9 (8H, br m, $(CH_2)_4$), 2.84 (1H, br s, OH), 3.30 (1H, d, J 13.2Hz, CH_AH_B pyridine), 3,59 (1H, d, J, 13.2Hz, CH_AH_B pyridine), 3.82 (3H, s, OMe), 4.65 (1H, br m OCH), 6.24 (1H, dd, J 3.3, 0.7Hz, furan H_3), 6.35 (1H, dd, J 3.3, 1.8Hz, furan H_4), 6.75-6.85 (3H, m, C_6H_3), 6.85 (2H, dd, J 4.5, 1.6Hz, pyridine H_3, H_5), 7.43 (1H, dd, J 1.8,

0.7Hz, furan $\underline{H}_5$), and 8.33 (2H, dd, $\underline{J}$ 4.5, 1.6Hz, pyridine $\underline{H}_2$, $\underline{H}_6$); $\underline{m/z}$ (ESI) 402 ($\underline{M}^+$+ 23, 20%), 380 ($\underline{M}^+$ + 1, 35), 287 (100), 95 (28), and 94 (97).

INTERMEDIATE 17

(3-Cyclopentyloxy-4-methoxyphenyl)-2-thienylmethanol

Thienyllithium (1.0$\underline{M}$ solution in THF; 14ml, 14.0mmol) was added to a solution of Intermediate 1 (3.04g, 13.8mmol) in THF (30ml) at -70°C. After 0.25h, the reaction mixture was allowed to warm to RT, stirred for 0.75h, then quenched with 10% aqueous NH_4Cl solution (25ml) and extracted with Et_2O (3x40ml). The extract was dried ($MgSO_4$), concentrated *in vacuo* , and the orange residue subjected to chromatography (SiO_2; Et_2O/hexane, 1:1) to afford the title compound (3.88g), as an off-white solid m.p. 79-80°C (from hexane-diisopropyl ether) (Found: C, 67.10; H, 6.65. $C_{17}H_{20}O_3S$ requires C, 67.08; H, 6.62%); δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(C\underline{H}_2)_4$), 2.37(1H, br s, O$\underline{H}$), 3.84 (3H, s, O$\underline{Me}$), 4.75 (1H, br m OC$\underline{H}$), 5.99 (1H, br s, C$\underline{H}$OH), 6.8-7.1 (5H, m, $C_6\underline{H}_3$ + thiophene $\underline{H}_3$, $\underline{H}_4$), and 7.2-7.3 (1H, m, thiophene $\underline{H}_5$) '$\underline{m/z}$ (ESI) 327 ($\underline{M}^+$+ Na, 100%).

INTERMEDIATE 18

(3-Cyclopentyloxy-4-methoxyphenyl)-2-thienylketone

A solution of Intermediate 17 (3.37g, 11.08mmol) in CH_2Cl_2 (200ml) was stirred vigorously with manganese (IV) oxide (15g) for 2h. The mixture was filtered through Celite® and the filtrate concentrated *in vacuo* to afford the title compound (3.32g), as an amber oil (Found: C, 67.38; H, 6.08. $C_{17}H_{18}O_3S$ requires C, 67.53; H, 6.00%); δ_H ($CDCl_3$) 1.55-2.0 (8H, br m, $(C\underline{H}_2)_4$), 3.93 (3H, s, O$\underline{Me}$), 4.85 (1H, br m, OC$\underline{H}$), 6.92 (1H, d, $\underline{J}$ 8.3Hz, Ar$\underline{H}$ *ortho* to OMe), 7.16 (1H, dd, 4.9, 3.8Hz, thienyl $\underline{H}_4$), 7.46 (1H, d, $\underline{J}$ 2.0Hz, Ar$\underline{H}$ *ortho* to cyclopentyloxy), 7.53 (1H, dd, $\underline{J}$ 8.3, 2.0Hz Ar$\underline{H}$ *para* to OMe), and 7.65-7.7 (2H, m, thienyl $\underline{H}_3$, $\underline{H}_5$); $\underline{m/z}$ (ESI) 627 (2$\underline{M}^+$+ Na, 90%), 325 ($\underline{M}^+$+ Na, 100), and 303 ($\underline{M}^+$, 10).

EXAMPLE 1

a) **(E) and (Z) Isomers of 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] pyridine**

Intermediate 7a (3.13g, 8.05mmol) was dissolved in toluene (70ml) containing 4-toluenesulphonic acid monohydrate (1.91g, 10.05mmol) and the mixture heated to reflux for 1h. The reaction mixture was poured into aqueous NaOH (10%; 100ml) and stirred for 5 min. The mixture was extracted with Et_2O (3x70ml) and the organic extract washed with water (80ml), and brine (80ml), then dried ($MgSO_4$), and concentrated *in vacuo* to afford a mixture of the title compounds (3.0g) as a viscous pale yellow oil. δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.82 (major) and 3.84 (minor) (3H, s, OMe), 4.8 (1H, br m, $OCHCH_2$), 6.6-7.4 (11H, m, ArH ortho to OMe + 2xArH meta to OMe + C_6H_5+ pyridine H_3, H_5), and 8.2 - 8.35 (2H, m, pyridine H_2, H_6); m/z 372 (M^+ + 1, 12%), 371 (M^+, 40), 304 (21), 303 (100), 302 (72) and 274 (22).

The following compounds were prepared using a similar procedure:

b) **(E) and (Z) Isomers of 2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] pyrazine**

From Intermediate 7b (570mg, 1.5mmol) and 4-toluene sulphonic acid (about 20mg). Upon completion, the reaction mixture was concentrated *in vacuo* then subjected to chromatography (SiO_2; Et_2O) to afford the title compound (520mg) as a colourless oil. δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.84 and 3.86 (3H, s, OMe), 4.58 and 4.72 (1H, br m, OCH), 6.65-7.5 (9H, m, C_6H_5+C=CH+ArH ortho to OMe+2xArH meta to OMe), 7.90 and 8.04 (1H, d, J 1.5Hz, pyrazine H_3), 8.18 and 8.21 (1H, d, J 2.5Hz, pyrazine H_6), and 8.45 and 8.48 (1H, m, pyrazine H_5).

c) **(E) and (Z) Isomers of 3-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] -2-methoxypyrazine**

From Intermediate 10a (2.94g, 7.0mmol) and 4-toluene-sulphonic acid (about 20mg) as described for Intermediate 7b to afford the title compound (2.67g) as a yellow oil. δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.80, 3.81, 3.83, 3.86 (2 x 3H, s, 2 x OMe), 4.50, 4.70 (1H, br m, OCH), 6.60-7.5 (9H, m, C_6H_5 + C = CH + ArH ortho to OMe + 2 x ArH meta to OMe) and 7.7-7.95 (2H, m, pyrazine H_5, H_6).

d) (i) **(E) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]-**

3,5-dichloropyridine

(ii) (Z) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]-3,5-dichloropyridine

From Intermediate 7c (1.60g, 3.58mmol) and 4-toluene-sulphonic acid (0.85g). Purification by column chromatography (SiO_2; CH_2Cl_2) afforded: i) (E) title compound (960mg) as an off-white solid m.p. 138.5-140°C. δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.72 (1H, br m, OCH), 6.59 (1H, s, C=CH), 6.85 (1H, d, J 8.4Hz, ArH ortho to OMe), 6.90 (1H, d, J 2.0Hz, ArH ortho to cyclopentyloxy), 6.95 (1H, dd, J 8.4, 2.0Hz, ArH para to cyclopentyloxy), 7.0-7.1 (2H, m, H_2, H_6 of C_6H_5), 7.15-7.3 (3H, m, H_3, H_4, H_5 of C_6H_5), and 8.35 (2H, s, pyridine H_2, H_6).

and ii) (Z) title compound (240mg) as an off-white solid. m.p. 155-156.5°C. δ_H ($CDCl_3$) 1.4-1.8 (8H, br m $(CH_2)_4$), 3.80 (3H, s, OMe), 4.42 (1H, br m OCH), 6.52 (1H, d, J 2.0 OHz,m ArH ortho to cyclopentyloxy), 6.56 (1H, s, C=CH), 6.57 (1H, dd, J 8.4, 2.0 Hz, ArH para to cyclopentyloxy), 6.68 (1H, d, J 8.4 Hz, ArH ortho to OMe), 7.3-7.45 (5H,m, C_6H_5), and 8.37 (2H, s, pyridine H_2, H_6).

e) (E) and(Z) Isomers of 2-[2-(3-Cyclopentyloxy-4-methoxy phenyl)-2-phenylethenyl]-4-methylpyridine

From Intermediate 10b (1.15g, 2.85mmol). Purification by chromatography (SiO_2; EtOAc) afforded the title compound (1.2g) as a pale yellow solid; δ_H ($CDCl_3$) 1.4-1.9 (8H, br m, $(CH_2)_4$), 2.04 (major), 2.09 (minor) (3H, s, pyridine Me), 3.85 (major), 3.88 (minor) (3H, s, OMe), 4.58 (minor), 4.72 (major) (1H, br m, OCH), 6.4-7.5 (11H, m, C_6H_5+C_6H_3+pyridine H_3, H_5 + C=CH), 8.5-8.55 (1H, m, pyridine H_6). ^{1}Hn.m.r indicates a 2:1 E/Z ratio.

f) (E) and (Z) Isomers of 4-[2-(3-Cyclopentyloxy-4-methoxy phenyl)-2-phenylethenyl]pyrimidine

From Intermediate 10c (2.55g). Purification by chromatography (SiO_2; Et_2O) afforded the title compound (1.20g) as a pale yellow foam; δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.88,3.90 (3H, s, OMe), 4.60, 4.70 (1H, br m, OCH), 6.44, 6.64 (1H, d, J 5.2Hz, pyrimidine H_5), 6.65-7.0 (3H, m, C_6H_3), 7.2-7.45 (6H, m, C_6H_5+C=CH), 8.26, 8.32 (1H, d, J 5.2Hz, pyrimidine H_6) , and 9.10, 9.12 (1H, ca s, pyrimidine H_2).

g) (E) and(Z) isomers of 3-[2-(3-Cyclopentyloxy-4-methoxy phenyl)-2-phenylethenyl]pyridazine

From Intermediate 10d (4.0g). Purification by chromatography (SiO_2; Et_2O) afforded the title compound (2.07g) as a pale yellow solid (Found: C, 77.59; H, 6.49; N, 7.24. $C_{24}H_{24}N_2O_2$ requires C, 77.39; H, 6.50; N, 7.52%); δ_H ($CDCl_3$) 1.5-1.9 (8H, br m, $(CH_2)_4$), 3.88 ,3.90 (3H, s, OMe), 4.58, 4.70 (1H, br m, OCH), 6.6-7.5 (11H, m, C_6H_5+C_6H_3+C=CH + pyridazine H_4, H_5+), and 8.85-8.90 (1H, m, pyridazine H_6) (^{1}Hnmr indicates a 3:2 E/Z ratio); m/z (ESI) 396 (M^++1+Na, 57%), 395 (M^++Na,100), 374 (66), 373 (78), and 305 (16).

EXAMPLE 2

(E) and (Z) isomers of 4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl] pyridine

A mixture of Intermediate 6 (0.48g,1.58mmol), Cs_2CO_3 (0.56g,1.73mmol), and cyclopentyl bromide (0.26g, 1.743mmol) in DMF (20ml) was stirred at RT overnight. A further portion of Cs_2CO_3 (0.20g,0.61mmol) and cyclopentyl bromide (0.28g, 1.86mmol) was added, the mixture stirred for 1.5h then concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; EtOAc/CH_3OH/Et_3N, 100:1:0.4) to afford the title compound (0.42g) as a white solid. m.p. 136-138°C (cyclohexane); δ_H ($CDCl_3$) 1.5-2.0 (8H, br m $(CH_2)_4$), 3.84 (3H, s, OMe), 4.65 (1H, br m $OCHCH_2$), 6.7-6.9 (6H, m, ArH *ortho* to OMe+2xArH *meta* to OMe+C=CH + pyridine H_3,H_5), 7.08 (2H, dd, *J* 4.5, 1.5 Hz, pyridine pyridine H_3', H_5'), 8.32 (2H, dm, *J* 5.0 Hz pyridine H_2, H_6), and 8.55 (2H, dd, *J* 4.5, 1.5Hz, pyridine H_2', H_6'); m/z 372 (M^+28%), 305 (37), 304 (100), 303 (95), 275 (18), and 41 (18)

EXAMPLE 3

a) (E) and (Z) isomers of 4-[2-(3-Cyclopentyloxy-4-methoxy phenyl)-2-phenylethenyl] phenol

A mixture of Intermediate 9 (2.94g, 10mmol), 4-bromophenol (2.16g, 12.5mmol), Et_3N (2.52g, 25mmol), tri-*o*-tolyl phosphine (0.06g, 0.2mmol) and palladium acetate (0.022g, 0.1mmol) was heated in a bomb at 140°C for 16h. Upon cooling, the reaction mixture was diluted with NH_4Cl (10%;

50ml) and CH_2Cl_2 (50ml). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (50ml). The combined organic layer was dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (SiO_2; hexane/Et_2O,1:1) yielded the title compound (1:1 mixture of isomers) (0.8g) as a yellow foam δ_H ($CDCl_3$) 1.2-1.9 (8H, br m, $(CH_2)_4$), 3.81, 3.83 (3H, s, OMe), 4.59, 4.69 (1H, br m, OCH), 5.5, 5.63 (1H, br s, OH), 6.55-7.0 (8H, m, C_6H_3+C_6H_4+C=CH), and 7.15-7.35 (5H, m, C_6H_5) [N.B. 'Hn.m.r. indicates ca 1:1E/Z mixture of isomers); m/z (ESI) 410 (M^++1+Na,18%), 409 (M^++Na,100) 387 (M^++1, 62), 319 (38), 318 (22), 301 (19), 236 (22), and 135 (20).

The following compounds were prepared using a similar procedure:

b) **(E) and (Z) Isomers of 3-[2-(3-Cyclopentyloxy-4-methoxy phenyl)-2-phenylethenyl] benzoic acid**

From Intermediate 9 (2.94g, 10mmol) and 3-bromobenzoic acid (5.03g, 25mmol). Purification by column chromatography [SiO_2;10%, CH_3OH/ CH_2Cl_2] furnished the title compounds (2g) as a viscous yellow oil. δ_H ($CDCl_3$) 1.45-2.0 (8H, br m, $(CH_2)_4$), 3.86, 3.87 (3H, s, OMe), 4.55, 4.7 (1H, br m, OCH), 6.65-8.25 (13H, m, C_6H_5+C_6H_4+C_6H_3+C=CH), (CO_2H not observed) [N.B. 'Hn.m.r. indicates ca 1:1E/Z mixture of isomers]; m/z (ESI) 437 (M^++23, 60%), 301 (67), 281 (100), and 259 (52).

c) **(E) and (Z) Isomers of 4-[2-(3-Cyclopentyloxy-4-methoxy phenyl)-2-phenylethenyl] anisole**

From Intermediate 9 (1.19g, 4.04mmol) and 4-bromoanisole (0.757g, 4.05mmol). Purification by column chromatography [SiO_2; hexane/Et_2O, 4:1] furnished the title compounds (0.78g) as a yellow oil. δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.72, 3.73 (3H, s, OMe), 3.82, 3.86 (3H, s, OMe), 4.58, 4.67 (1H, br m, OCH), 6.6-6.9 (6H, m, C_6H_3+2xArH ortho to OMe+C=CH), 6.93, 7.00 (2H, d, J 8.5Hz, 2xArH meta to OMe) and 7.15-7.35 (5H, m, C_6H_5) [N.B. 'Hn.m.r. indicates ca 1:1E/Z mixture of isomers]; m/z (ESI) 424 (M^++1+Na, 20%), 423 (M^++Na, 100%), 374 (12), 281 (20), 198 (12), 132 (12) and 86 (12).

d) **(E) and (Z) isomers of Methyl 4-[2-(3-Cyclopentyloxy-4-**

methoxyphenyl)-2-phenylethenyl]benzoate

From Intermediate 9 (2.94g, 10mmol) and methyl 4-bromobenzoate (2.69g, 12.5mmol) to afford the title compounds (3.35g) as a yellow gum; δ_H ($CDCl_3$) 1.4-2.0 (8H, br m, $(CH_2)_4$), 3.86, 3.87 (6H, s, OMe+CO_2Me), 4.54, 4.67 (1H, br m, OCH), 6.6-7.4 (11H, m, C_6H_5+C_6H_3+C=CH+2xArH meta to CO_2Me), and 7.75-7.85 (2H, m, 2xArH ortho to CO_2Me) [N.B. ^{1}Hn.m.r. indicates ca 1:1E/Z mixture of isomers]; m/z (ESI) 429 (M^++1+Na, 28%), 362 (18), 361 (28), 330 (70), and 329 (68).

e) **(E) and (Z) Isomers of 3-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]pyridine**

From Intermediate 9 (1.00g, 3.4mmol) and 3-bromopyridine (1.28g, 8.1mmol). Purification by chromatorgaphy (SiO_2; Et_2O) afforded the title compound (0.50g) as a pale yellow gum; δ_H ($CDCl_3$) 1.45-2.0 (8H, br m, $(CH_2)_4$), 3.85 (major), 3.87 (minor) (3H, s, OMe), 4.55 (minor), 4.69 (major) (1H, br m, OCH), 6.65-7.5 (11H, m, C_6H_5+C_6H_3+pyridine H_4,H_5+C=C), and 8.2-8.45 (2H, m, pyridine H_2,H_6).

EXAMPLE 4

(E) and (Z) Isomers of 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] acetoxybenzene

To a stirred solution of the compound of Example 3a (0.2g, 0.52mmol) in CH_2Cl_2 (5ml), under a nitrogen atmosphere, was added Et_3N (0.101g, 0.14ml, 1mmol) followed by acetyl chloride (0.0785g, 0.071ml, 1mmol). The reaction mixture was stirred at RT for 4h then poured into saturated $NaHCO_3$ (10ml). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to furnish the title compounds (0.222g) as a colourless oil. δ_H ($CDCl_3$) 1.5-1.9 (8H, br m, $(CH_2)_4$), 2.23, 2.24 (3H, s, OCOMe), 3.83, 3.86 (3H, s, OMe), 4.56, 4.67 (1H, br m, OCH), and 6.7-7.4 (13H, m, C_6H_5+C_6H_4+C_6H_3+C=CH) [N.B. ^{1}Hn.m.r. indicates ca 1:1E/Z mixture of isomers]; m/z (ESI) (M^++Na, 100%), 319 (20), 281 (29), 191 (48), 127 (50) and 55 (54).

EXAMPLE 5

(E) and (Z) isomers of Methyl 3-[2-(3-cyclopentyloxy-4-methoxy

phenyl)-2-phenylethenyl]benzoate

To a cold (0°C) solution of the compound of Example 3b (0.25g, 0.6mmol) in CH_3OH (20ml) was added $SOCl_2$ (0.357g,0.22ml,3mmol) dropwise and the reaction mixture was stirred at RT for 3h. The solvent was evaporated *in vacuo*, the residue dissolved in CH_2Cl_2 (20ml) and washed with saturated $NaHCO_3$ (20ml). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (20ml). The combined organic layer was dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to yield the title compound (0.215g) as a yellow oil. δ_H ($CDCl_3$) 1.4-2.0 (8H, br m, $(CH_2)_4$), 3.82, 3.83, 3.84, 3.85 (6H, s, OMe + CO_2Me), 4.54, 4.69 (1H, br m, OCH), and 6.65-7.85 (13H, m, C_6H_5+C_6H_4+C_6H_3+C=CH) [N.B. ^{1}Hn.m.r. indicates *ca* 1:1E/Z mixture of isomers]; *m/z* (ESI) 429 (M^++1, 25%), 361 (22), 329 (100), 159 (12), 102 (15), and 60 (75).

EXAMPLE 6

(E) and (Z) Isomers of 4-[2-(4-Aminophenyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine

Water (15ml) and trifluoroacetic acid (10ml) were added to Intermediate 13 (6.1g) in CH_2Cl_2 (15ml) at 0°C and the mixture allowed to warm to RT. After 6h, the reaction mixture was concentrated *in vacuo* and the residue partitioned between 10% hydrochloric acid (50ml) and EtOAc (50ml). The aqueous layer was separated, basified to pH 14 with 20% sodium hydroxide solution, and extracted with CH_2Cl_2 (3x50ml). The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude title compound (4.2g). A portion (0.40g) was subjected to chromatography (SiO_2); EtOAc) to afford the title compound (0.29g); δ_H ($CDCl_3$) 1.45-2.0 (8H, br m, $(CH_2)_4$), 3.80 (2H, br s, NH_2), 3.87, 3.90 (3H, s, OMe), 4.58, 4.70 (1H, br m, OCH), 6.6-7.2 (10H, C_6H_4+ C_6H_3+pyridine H_3, H_5+C=CH), and 8.3-8.4 (2H, m, pyridine H_2,H_6); *m/z* (ESI) 388 (M^++1, 100%).

EXAMPLE 7

a) (E) and (Z) isomers of 4-[2-(4-Bromophenyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine

A solution of Intermediate 7d (7.52g, 16.0mmol) and triethylamine (4.05g, 5.60ml, 40.0mmol) in CH_2Cl_2 (100ml) was cooled to 0°C and trifluoroacetic anhydride (3.70g, 2.50ml, 17.6mmol) was added dropwise.

The orange-red solution was allowed to warm to RT over 20h then water (25ml) was added. The mixture was extracted with CH_2Cl_2 and the extract was dried ($MgSO_4$), concentrated *in vacuo* and subjected to chromatography to give the title compound (4.73g) as a white amorphous powder. (Found: C, 66.66; H, 5.27; N, 2.99. $C_{25}H_{24}BrNO_2$ requires C, 66.67; H, 5.37; N, 3.11%); δ_H ($CDCl_3$) 1.45-1.95 (8H, br, m, $(CH_2)_4$), 3.86, 3.88 (3H, s, OMe), 4.55, 4.70 (1H, br m, OCH), 6.6-6.95 (6H, m, C_6H_3, + pyridine H_3, H_5) + C=CH), 7.06, 7.21 (2H, d, J 8.4Hz, ArH of C_6H_4), 7.4-7.5 (2H, m, ArH of C_6H_4), and 8.36 (2H, ca. d, J 6.0Hz, pyridine H_2, H_6) (^{1}H n.m.r. indicates a 1:1 E/Z mixture); ν_{max} ($CDCl_3$) 1597, 1514, and 1251 cm^{-1}; m/z (ESI) 452 (M^+ + 2 + Na, 100%), 450 (M^+ +Na, 88), 384 (30) and 382 (28).

The following compound was prepared to a manner similar to compound of example 7a.

b) **(Z)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-furyl) ethenyl]pyridine**

From the compound of Intermediate 15 (1.0g, 2.64mmol) in CH_2Cl_2 (30ml), triethylamine (0.4g, 0.55ml, 3.96mmol) and trifluoroacetic anhydride (0.61g, 0.41ml, 2.91mmol). Work up [includes treatment with 10% NaOH solution (25ml)] and chromatography (SiO_2; EtOAc/hexane, 7:3) afforded the title compound (0.78g) as a pale pink solid m.p. 122-123°C; (Found: C, 76.37; H, 6.46; N, 3.85. $C_{23}H_{43}NO_3$ requires C, 76.43; H, 6.41; N, 3.88%) ;δ_H ($CDCl_3$) 1.45-1.9 (8H, br m, $(CH_2)_4$), 3.90 (3H, s, OMe), 4.65 (1H, br m, OCH), 6.07 (1H, d, J 3.3Hz, furan H_3), 6.41 (1H, dd, J 3.3, 1.8Hz, furan H_4), 6.75-6.9 (5H, m, C_6H_3 + pyridine H_3, H_5), 7.03 (1H, s, C=CH), 7.49 (1H, d, J 1.6Hz, furan H_5), and 8.33 (2H, ca. d, J 4.6Hz, pyridine H_2, H_6); m/z (ESI) 362 (M^+ +1, 100%), 294 (45).

EXAMPLE 8

(E) and (Z) isomers of -4-[-1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl]benzoic acid hydrochloride

Intermediate 15 (4.25gm 8.8mmol) in 10% aqueous HCl (15ml) was heated to reflux for 20 min. Aqueous NaOH solution (5M; 20ml) and EtOH (15ml) were then added and heating continued for a further 2h. The

concentrated *in vacuo* to afford the title compound (115mg) as a colourless gum; δ_H ($CDCl_3$) 1.5-1.9 (8H, br m, $(CH_2)_4$), 3.84, 3.86 (3H, s, OMe), 4.56,4.67 (1H, br m, OCH), and 6.65-7.4 (13H, m, C_6H_3 + C_6H_4 + C_6H_5 + C=CH); m/z (ESI) 390 (M^+ + 2, 23%), 389 (M^++1, 92), 253 (37), and 235 (100).

The following compound was prepared in a manner similar to the compound of Example 10a.

b) **(E) and (Z) Isomers of 4-[2-(4-chlorophenyl)-1-phenylethenyl]-2-cyclopentyloxyanisole**

From Intermediate 2 and diethyl 4-chlorobenzylphosphonate to afford the title compound as a clear oil. δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.86, 3.89 (3H, s, OMe), 4.57,4.70 (1H, br m, OCH), and 6.65-7.4 (13H, m, C_6H_3 + C_6H_4 + C_6H_5 + C=CH) (^{1}Hn.m.r. indicates ca 1:1 E:Z ratio); m/z (ESI) 429 (M^+ + 2 + Na, 15%), 427 (M^++Na, 45), 387 (30), 386 (100), 301 (25), and 60 (20).

FORMULATION EXAMPLES

The compounds of the invention may be formulated for pharmaceutical use in a number of forms using any suitable excipients. Thus, for example, for oral use the compounds of the invention such as the compounds of the Examples may be formulated as a solid dosage form, by mixing an appropriate weight of compound (for example 50mg) with maize starch (50-99%w/w), anhydrous colloidal silica (0-10%w/w) and organic or inorganic acid (up to 1%w/w), to fill capsules of an appropriate size, e.g. white opaque hard gelatine capsules size 3. If desired the same mixture may be compressed into tablets.

The activity and selectivity of compounds according to the invention was demonstrated in the following tests. In these tests the abbreviation FMLP represents the peptide N-formyl-met-leu-phe.

Isolated Enzyme

The potency and selectivity of the compounds of the invention was determined using distinct PDE isoenzymes as follows:

i. PDE I, rabbit heart
ii. PDE II, rabbit heart
iii. PDE III, rabbit heart, Jurkat cells
iv. PDE IV, HL60 cells, rabbit brain, rabbit kidney and human recombinant PDE IV
v. PDE V, rabbit lung, guinea pig lung

A gene encoding human PDE IV has been cloned from human monocytes (*Livi, et al., 1990, Molecular and Cellular Biology, 10, 2678*). Using similar procedures we have cloned human PDE IV genes from a number of sources including eosinophils, neutrophils, lymphocytes, monocytes, brain and neuronal tissues. These genes have been transfected into yeast using an inducible vector and various recombinant proteins have been expressed which have the biochemical characteristics of PDE IV (*Beavo and Reifsnyder, 1990, TIPS, 11, 150*). These recombinant enzymes, particularly the human eosinophil recombinant PDE IV, have been used as the basis of a screen for potent, selective PDE IV inhibitors.

The enzymes were purified to isoenzyme homogeneity using standard chromatographic techniques.

Phosphodiesterase activity was assayed as follows. The reaction was conducted in 150μl of standard mixture containing (final concentrations): 50mM 2-[[tris(hydroxymethyl)methyl]amino]-1-ethane-sulphonic acid (TES) -NaOH buffer (pH 7.5), 10mM $MgCl_2$, 0.1μM [^{3}H]-cAMP and vehicle or various concentrations of the test compounds. The reaction was initiated by addition of enzyme and conducted at 30^{o}C for between 5 to 30 mins. The reaction was terminated by addition of 50μl 2% trifluoroacetic acid containing [^{14}C]-5'AMP for determining recovery of the product. An aliquot of the sample was then applied to a column of neutral alumina and the [^{3}H]-cAMP eluted with 10ml 0.1 TES-NaOH buffer (pH8). The [^{3}H]-5'-AMP product was eluted with 2ml 2M NaOH into a scintillation vial containing 10ml of scintillation cocktail. Recovery of [^{3}H]-5'AMP was determined

using the [^{14}C]-5'AMP and all assays were conducted in the linear range of the reaction.

Compounds according to the invention such as compounds of the Examples herein cause a concentration-dependent inhibition of recombinant PDE IV at 0.1 - 1000nM with little or no activity against PDE I, II, III or V at concentrations up to 100μM.

2. **The Elevation of cAMP in Leukocytes**

The effect of compounds of the invention on intracellular cAMP was investigated using human neutrophils or guinea pig eosinophils. Human neutrophils were separated from peripheral blood, incubated with dihydrocytochalasin B and the test compound for 10 min and then stimulated with FMLP. Guinea pig eosinophils were harvested by peritoneal lavage of animals previously treated with intra-peritoneal injections of human serum. Eosinophils were separated from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific radioimmunoassay (DuPont).

The most potent compounds according to the Examples induced a concentration -dependent elevation of cAMP in neutrophils and/or eosinophils at concentrations of 0.1nM to 1μM.

3. **Suppression of Leukocyte Function**

Compounds of the invention were investigated for their effects on superoxide generation, chemotaxis and adhesion of neutrophils and eosinophils. Isolated leukocytes were incubated with dihydrocyto-chalasin B for superoxide generation only and test compound prior to stimulation with FMLP. The most potent compounds of the Examples caused a concentration-dependent inhibition of superoxide generation, chemotaxis and adhesion at concentrations of 0.1nM to 1μM.

Lipopolysaccharide (LPS)-induced synthesis of tumour necrosis factor (TNF) by human peripheral blood monocytes (PBM) is inhibited by compounds of the Examples at concentrations of 0.01nM to 10μM.

4. **Relaxation of Constricted Airway Smooth Muscle in vitro**

The effects of compounds of the invention on guinea-pig isolated tracheal smooth muscle were investigated. Isolated tracheal rings were suspended in organ baths and immersed in oxygenated Krebs' solution. The smooth muscle was contracted with sub-maximal concentrations of histamine or carbachol prior to the addition of increasing concentrations of test compound to the organ baths. The most potent compounds of the Examples caused a concentration-dependent reversal of both histamine and carbachol-induced contractions at concentrations of 1nM to 100μM. The compounds were generally more potent in reversing histamine-induced tone than carbachol-induced tone.

5. **Effects on Cardiac Muscle in vitro**

Compounds of the invention have been tested for their effects on isolated cardiac muscle. Right atrial and papillary muscles were dissected out from the hearts of guinea pigs and suspended in organ baths for measuring the rate (chronotropic) of spontaneously beating atria and force (inotropic) of the electrically stimulated papillary muscle. In these preparations, selective PDE IV inhibitors such as rolipram do not have any direct effects whereas selective PDE III inhibitors such as milrinone have positive chronotropic and inotropic effects. The non-specific PDE inhibitor theophylline, which is used in asthma as a bronchodilator, also causes significant cardiovascular changes such as tachycardia. Selective PDE IV inhibitors have advantage over theophylline, therefore, through reduced cardiovascular side effects. The most potent and selective compounds of the Examples had no direct effects on the atrial and papillary muscles <u>in vitro</u> at concentrations up to 10μM but in combination with PDE III inhibitors, these inhibitors showed an enhancement of chronotropic and inotropic activity, typical of selective type IV inhibitors.

6. **Anti-Inflammatory Activity in vivo**

Interleukin-5 (IL-5)-induced pleural eosinophilia in the rat (*Lisle, et al, 1993, Br.J. Pharmacol. 108, 230p*) is inhibited by compounds of the Examples given orally at doses of 0.0001 to 10.0mg/kg. The most potent compounds cause a dose-dependent reduction in migrating eosinophils with ED_{50}s of 0.003 to 0.03mg/kg p.o.

Compounds of the invention also reduce the inflammatory responses induced in rats by platelet activating factor (PAF).

7. **Anti-allergic Activity in vivo**

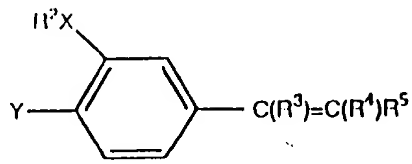
Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitised guinea pigs. Guinea pigs were initially sensitised to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminium hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later and at six weeks, animals were challenged with aerosolised ovalbumin whilst under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of the Examaples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

8. **Effects on Pulmonary Dynamics**

Compounds of the invention (0.001-10mg/kg by oral or other route of aministration) reduce the allergic bronchoconstruction caused by antigen in sensitized guinea pigs.

CLAIMS

1. A compound of formula (1)



(1)

wherein Y represents a halogen atom or a group OR^1, where R^1 is an optionally substituted alkyl group;
X is -O-, -S- or $-N(R^6)-$, where R^6 is a hydrogen atom or an alkyl group;
R^2 is an optionally substituted alkyl, alkenyl, cycloalkyl or cycloalkenyl group;
R^3 and R^4, which may be the same or different, is each a group $-(CH_2)_nAr$, where Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms and n is zero or an integer 1, 2 or 3;
R^5 is a hydrogen atom or an optionally substituted alkyl group; and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein X is -O-.

3. A compound according to Claim 1 or Claim 2, wherein Y is a group $-OR^1$ where R^1 is a methyl group.

4. A compound according to any one of Claim 1 to Claim 3 wherein R^2 is a cyclopentyl group.

5. A compound according to any one of Claim 1 to Claim 4 wherein Y is a $-OCH_3$ group, X is -O-, R^2 is a cyclopentyl group and wherein R^3 and R^4 is each independently a group -Ar.

6. A compound according to Claim 5 wherein R^3 is a group Ar where Ar is an unsubstituted or substituted monocyclic aryl or monocyclic nitrogen-containing heteroaryl group and R^4 is a group Ar where Ar is an unsubstituted or substituted monocyclic nitrogen-containing heteroaryl group.

7. A compound according Claim 6 wherein the monocyclic aryl group is an unsubstituted or substituted phenyl group, the monocyclic heteroaryl group is an unsubstituted or substituted furyl or thienyl group and the monocyclic nitrogen-containing heteroaryl group is an unsubstituted or substituted pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group.

8. A compound according to Claim 7 wherein the nitrogen-containing heteroaryl group is a substituted or unsubstituted pyridyl group.

9. A compound according to Claim 1 selected from the (E) and (Z) isomers of:
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-furyl) ethenyl]pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-thienyl)ethenyl] pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]-3-methylimidazole;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]pyridine;
4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl] pyridine;
(4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-fluorophenyl-ethenyl] pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-trifluoromethyl-phenyl)ethenyl]pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-methoxyphenyl-ethenyl)]pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-ethenyl]pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-methylphenyl)

ethenyl]pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-methylphenyl)-ethenyl]pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]-3,5-dichloropyridine;

2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]pyridine;

4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl] aniline;

4-[1-(3-Cyclopenxyloxy-4-methoxyphenyl0-2-(4-pyridyl)ethenyl] benzoic acid;

Ethyl N-{4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl) ethenyl]phenyl}carbamate;

N-{4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2(4-pyridyl)ethenyl] phenyl}N'-ethylurea;

N-{4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)]-2-(4-pyridyl)ethenyl} phenylacetamide;

3-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl]pyridine;

4-[2-2(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] pyrimidine;

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-hydroxymethyl-phenyl)ethenyl]pyridine;

4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl] benzamide;

Ethyl-4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-phenyl-ethenyl]benzoate;

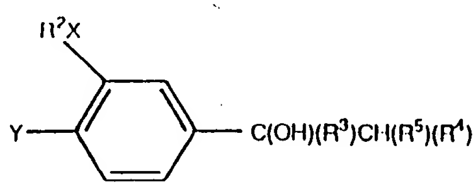
N-{4-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethenyl] phenyl}methanesulphonamide; or

each (E) or (Z) isomer thereof; and the salts, solvates, hydrate and N-oxides thereof.

10. A pharmaceutical composition comprising a compound of formula (1):

containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms and n is zero or an integer 1, 2 or 3;
R^5 is a hydrogen atom or an optionally substituted alkyl group; and the salts, solvates, hydrates and N-oxides thereof which comprises in a final step

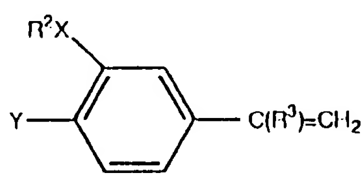
a) a dehydration of a compound of formula (3):



(3)

wherein Y, X, R^2, R^3, R^4, and R^5 are as defined for formula (1), to yield a compound of formula (1); or

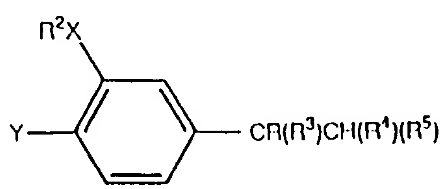
b) coupling a compound of formula (11)



(11)

wherein Y, R^2 and R^3 are as defined for formula (1) in a Heck reaction, with an organopalladium compound derived from a compound R^4Hal; or

c) the dehydrogenation of a compound of formula (12):



(12)

where R is a hydrogen atom

wherein Y, X, R^2, R^4 and R^5 are as defined for formula (1) to yield a compound of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom; or

d) the interconversion of a compound of formula (1) to another compound of formula (1);

e) by reaction of a compound of formula (1) with an acid or base to yield a salt of a compound of formula (1); or

f) by deprotection of a corresponding protected compound of formula (1).

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL ABSTRACTS, vol. 118, 1993, Columbus, Ohio, US; abstract no. 136183z, HIROSE ET AL 'Styrene derivatives and electrophotographic photoreceptor containing them' page 793 ; see abstract & JP,A,4 287 049 (KONICA CO) 12 October 1992	1-3
X	CHEMICAL ABSTRACTS, vol. 93, 1980, Columbus, Ohio, US; abstract no. 95160j, MEZHERITSKAYA L. V ET AL 'Synthesis and properties of carboxonium heterocyclic systems' page 635 ; see abstract & ZH. ORG. KHIM. vol. 16, no. 1, 1980, pages 183 - 188 MEZHERITSKAYA ET AL	1-3
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 29, no. 8, 1986, pages 1355 - 1362 M.R.SCHNEIDER ET AL 'Catechol estrogens of the 1,1,2-triphenylbut-1-ene type' *see compounds 16,18-23*	1-3
X	DE,A,2 501 443 (LABORATOIRES PHARMASCIENCE.) 24 July 1975 *see compound on page 13, beispiel 4*	1-3
A	WO,A,9 200 968 (SMITH-KLINE BEECHAM CORPORATION) 23 January 1992 see the whole document	1-11
A	WO,A,9 115 451 (SMITH-KLINE BEECHAM CORPORATION) 17 October 1991 see the whole document	1-10
A	EP,A,0 490 823 (SANDOZ LTD.) 17 June 1992 see the whole document	1-10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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		US-A- 5177085	05-01-93